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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:

David Frederick HORROBIN

Serial No.: 09/898458 Group Art Unit: 1615

Filed: July 5, 2001

For: VITAMIN K AND ESSENTIAL FATTY ACIDS

CLAIM OF PRIORITY
UNDER 35 U.S.C. § 119

Commissioner of Patents
Washington, D.C. 20231

Sir:

The benefit of the filing date of prior foreign application No. 0016452.5 filed in New Zealand on July 4, 2000, is hereby requested and the right of priority provided in 35 U.S.C. §119 is hereby claimed.

In support of this claim, filed herewith is a certified copy of said original foreign application.

Respectfully submitted,

JACOBSON HOLMAN, PLLC

By: _____
John C. Holman
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400 Seventh Street, N.W.
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Atty. Docket No.: P66731US0
Date: November 2, 2001

The Patent Office

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an amendment, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

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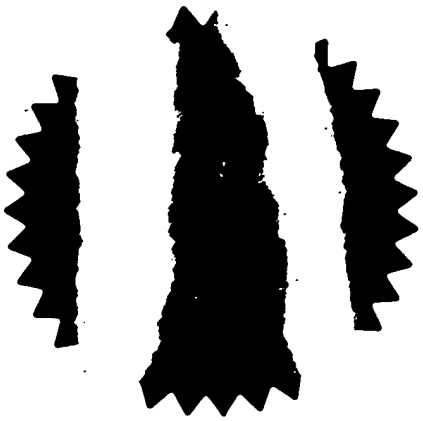

Signed P. Mahoney

Dated 18 October 2001

Patents Form 1/77

Patents Act 1977
(Rule 16)

The Patent Office

1/77

05JUL00 E550315-2 D01631
P01/7700 0.00-0016452.5

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form.)

The Patent Office
Cardiff Road
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Gwent NP9 1RH

Fee: £0

1. Your reference — 42105/HRW

2. Patent application number *(The Patent Office will fill in this part)* — 04 JUL 2000 — 0016452.5

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Kilgowan Limited
c/o Simcocks See A/C dd 4/8/00.
PO Box 181
Ridgeway House
Ridgeway St,
Douglas,
Isle of Man IM99 1PY

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of incorporation — Isle of Man — 7626930001

4. Title of the invention

Vitamin K and Essential Fatty Acids

5. Full name, address and postcode in the United Kingdom to which all correspondence relating to this form and translation should be sent

Reddie & Grose
16 Theobalds Road
LONDON
WC1X 8PL

Patents ADP number *(if you know it)* — 91001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application *(If you know it)*	Date of filing *(day/month/year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day/month/year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
   a) any applicant named in part 3 is not an inventor, or
   b) there is an inventor who is not named as an applicant, or
   c) any named applicant is a corporate body.
   See note (d))

YES

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document.

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Description	12
Claim(s)	3
Abstract	-
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	-
Request for preliminary examination and search *(Patents Form 9/77)*	-
Request for substantive examination *(Patents Form 10/77)*	-
Any other documents *(please specify)*	-

11. I/We request the grant of a patent on the basis of this application.

Signature

Date
4 July 2000

12. Name and daytime telephone number of person to contact in the United Kingdom

C R BAKERLEY
020 7242 0901

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VITAMIN K AND ESSENTIAL FATTY ACIDS

Vitamin K is a general name for a group of compounds all with similar biological activity. They all contain the 2-methyl-1,4-naphthoquinone nucleus with a lipophilic side chain at position 3. The three best known members are phylloquinone (vitamin K1) which is the only type of vitamin K found in plants. Vitamin K2, the menaquinones, consists of a family of compounds with variable length isoprenyl side chains. Vitamin K3, menadione, is a pro-vitamin which can be converted to vitamin K2 by animals. Menadione and the menaquinones may occasionally have toxic effects in high doses whereas phylloquinone seems to be safe even in massive overdose. Phylloquinone is therefore the preferred form of the vitamin for human use.

Vitamin K compounds are widely distributed in foods. Among animal foods, eggs, butter and liver are good sources and contain amounts of from about 2 to about 50 μg/100g of the food. Green vegetables are also good sources and may contain from 30 to as much as 800 μg/100g of the food. Spinach, kale, sprouts and broccoli are good sources. Vegetable oils, and products made from vegetable oils such as margarines and salad dressings, can also be good sources, containing from 10 to 300 μg of vitamin K per 100g of oil. Olive oil and soy oil are particularly rich in vitamin K. Some vitamin K is also made from gut bacteria although this is difficult to quantitate and may be very variable.

The US Recommended Daily Allowance (RDA) for vitamin K starts at 10 μg/day for infants and rises to

65 μg/day in women and 80 μg/day in men. There is, however, evidence that vitamin K from some foods may be relatively poorly absorbed and there have been suggestions that these RDAs for ordinary foods may be somewhat low (BLMG Gijsbers et al, Effect of food composition on vitamin K absorption in human volunteers, Br J Nutrition 1996; 76: 223-229).

The best known role for vitamin K in humans is as a co-factor for the synthesis of six of the proteins involved in blood clotting. These proteins are inactive proenzymes which are converted to active enzymes in the presence of calcium during the coagulation process. These proteins contain an unusual amino acid, gamma-carboxy-glutamate. This is formed by the carboxylation of glutamic acid residues in the protein by the enzyme gamma-glutamyl carboxylase, in a vitamin-K dependent reaction. In the absence of vitamin K, the normal forms of the clotting factors cannot be synthesised. Proteins containing gamma-carboxy-glutamate have become known by the general name of Gla proteins.

For some time it was thought that Gla proteins were confined to the clotting system and it was largely on this basis that the RDAs were estimated. However, it is now known that enzymes with gamma-glutamyl-carboxylase activity are widely distributed in many different tissues and so it is probable that there are many functions of Gla proteins to be discovered. These proteins are particularly abundant in kidney and in bone and so it is assumed that they have particular roles to play in these organs. Two Gla proteins are particularly abundant in bone. Bone Gla

protein (BGP, commonly known as osteocalcin) contains three Gla residues and is present in great abundance in bone, dentin and cartilage. Matrix Gla protein (MGP) is also found in substantial amounts in bone, dentin and cartilage. Much ongoing research is trying to identify the roles of these proteins which seem to be involved in determining the strength and resilience of the structure. The kidney Gla proteins may be involved in regulation of calcium excretion so that vitamin K may play a role in integrating the various mechanisms involved in maintaining bone strength (NC Binkley and J W Suttie, Vitamin K nutrition and osteoporosis, J Nutr 1995; 125: 1812-21 and C Vermeer et al, Effects of vitamin K on bone mass and bone metabolism, J Nutr 1996; 126: 1187S-1191S).

Recently there is evidence that vitamin K can have clinically relevant effects on bone. In women with osteoporosis, a controlled study showed that 45mg/day of vitamin K2 could reduce the risk of bone fractures and slow down but not prevent a progressive loss of bone mineral density (M Shiraki et al, J Bone Mineral Res 2000; 15: 515-521). In a prospective study of 72,000 nurses, women with the lowest quintile of vitamin K intake (109 μg/day and below) had an increased risk of fractures D Feskanich et al, Vitamin K intake and hip fractures in women: a prospective study, Am J Clin Nutr 1999; 69: 74-79). In an older group of men and women, mostly over 70, there was a progressively reducing risk of osteoporotic fracture as vitamin K intake increased. The lowest risk was in the highest quartile of vitamin K intake of more than 262 μg/day in women and

more than 234 μg/day in men (SL Booth et al, Dietary vitamin K intakes are associated with hip fracture but not with bone mineral density in elderly men and women, Am J Clin Nutr 2000; 71: 1201-8). The progressive effect of increasing daily intakes suggests that doses of vitamin K much higher than the RDAs may be important in bone health, especially in older people.

The essential fatty acids (EFAs) are a completely different group of nutrients. There are two types; the omega-6 derived from the parent linoleic acid, and the omega-3 derived from the parent alpha-linolenic acid (figure 1). The EFAs cannot be synthesised de novo by humans or other mammals. Nor can mammals convert omega-3 EFAs into omega-6 EFAs or vice versa. Mammals can interconvert one omega-6 EFA into another omega-6 EFA via the pathways shown in figure 1. Similarly, omega-3 EFAs can be converted one to another. The pathways shown in figure 1 usually progress from linoleic acid or alpha-linolenic acid downwards, but retro-conversions are possible.

The EFAs are essential components of complex lipids such as triglycerides, cholesterol esters and phospholipids, and are absolutely required for the normal structure and function of all cell and other membranes in the body. Deficiencies of EFAs cause widespread defects in all body systems. While dietary deficiencies of the parent EFAs, linoleic and alpha-linolenic acids are relatively rare, deficiencies of their metabolites are relatively common because of impaired conversion mechanisms. As a result low

levels of fatty acids like dihomogammalinolenic acid (DGLA), arachidonic acid (AA) and adrenic acid (AdrA) of the n-6 series and of stearidonic acid (SA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) of the n-3 series have been commonly reported. Such low levels have been found in skin diseases including atopic eczema; reproductive system disorders including premenstrual syndrome, breast pain and menstrual pain; diabetes; cardiovascular disorders; bone disorders; kidney diseases; psychiatric diseases including schizophrenia, depression, stress and attention deficit hyperactivity disorder; and many other conditions. Treatment with EFAs, especially with gamma-linolenic acid (GLA) of the n-6 series and with EPA and DHA of the n-3 series has been reported to be associated with a wide range of beneficial effects. These effects have been reported to be enhanced by certain nutrients such as zinc and vitamin B6 which are important in EFA metabolism.

The present invention is based on the inventor's finding of a completely unexpected and hitherto unreported interaction between vitamin K and EFAs.

The present invention provides nutritional and pharmaceutical formulations comprising in combination a source of vitamin K and a source of at least one essential fatty acid (EFA), in which the concentration of vitamin K is not less than 1000 μg/100g. Preferably, the concentration of vitamin K is not less than 100 μg/10g. The formulations of the invention preferably comprise between 50 μg and 100 mg vitamin K and between 50 mg and 100 g of the EFA.

These are to provide a daily dose of these amounts and the formulation may be in the form of a single dosage, to provide these intakes in one go, or in the form of divided doses.

Vitamin K is preferably in the form of phylloquinone (vitamin K1).

The EFA may be selected from the n-6 series: gamma-linolenic acid, dihomogammalinolenic acid, arachidonic acid and adrenic acid, and combinations of these EFAs. Alternatively, the EFA is selected from the n-3 series: stearidonic acid, eicosapentaenoic acid, docosapentaenoic acid and docosahexaenoic acid, and combinations of these EFAs. In a further embodiment of the present invention at least one n-6 EFA is present with at least one n-3 EFA, each EFA selected from the above lists.

The active ingredient of the nutritional or pharmaceutical composition may consist essentially wholly of EFA and vitamin K or, alternatively, the formulations of the present invention may further comprise one or more essential vitamins and/or minerals or one or more pharmaceutical drugs.

The present invention further provides foodstuff which already contain EFAs to which have been added vitamin K in an amount to raise the vitamin K content of the food to 1000 μg / 100 g food, or more. The specific EFA(s) content may also be raised artificially by the addition of one of more EFAs.

The present invention still further provides foodstuff which naturally contains clinically or nutritionally small amounts of vitamin K and / or EFA(s) but to which has been added vitamin K and EFAs, for example to the dosage regime of the formulations of the first aspect of the present invention. Milk and other dairy products or simulated dairy products are particularly appropriate for this type of enrichment.

The foodstuffs and nutritional or pharmaceutical formulations of the present invention may be used to treat or prevent a variety of diseases or conditions. These may include:

premenstrual or menstrual disorders of any kind;

bone or calcium disorders of any kind, including osteoporosis;

metabolic or cardiovascular disorders including diabetes, obesity, elevated blood cholesterol or triglyceride levels or cardiovascular disorders;

stress, mental, psychological, psychiatric or neurological disorders;

skin disorders;

asthma or other respiratory disorder;

arthritis or any form of inflammatory, gastrointestinal, kidney or reproductive system disorder.

The present invention further provides a method of treatment or prevention of diseases or conditions, including those mentioned above, by the administration of a combination of vitamin K and an EFA, preferably at the dosage rate of between 50 μg

and 100 mg vitamin K and between 50 mg and 100 g EPA. In particular, the disorders to be treated are skin disorders and premenstrual or menstrual conditions. Bone disorders are also of particular importance.

The vitamin K may be provided in any form which has biological vitamin K activity in mammals. However, because of its safety and known activity, vitamin K1 (phylloquinone) is the preferred form. The formulations may provide for an increase in vitamin K intake in a nutritional or pharmaceutical formulation or food of from 50 μg to 100 mg per day. At the same time the formulations should provide for an increase in the intake of one or more of the desired EFAs of between 50mg and 50g per day. Depending on the problem to be addressed, any of the EFAs shown in figure 1 may be used. Linoleic acid, alpha-linolenic acid, GLA, DGLA, AA, AdrA, SA, EPA, DPA and DHA are likely to be preferred ingredients for particular purposes. The EFAs may be provided as purified or partially purified compounds or may be supplied by natural oils which are rich in one or more EFAs. For example, borage and evening primrose oils are good sources of GLA, Echium oils are good sources of SA, marine oils are often good sources of EPA, DPA, DHA and sometimes AA, while oils from various microbial sources, including fungal and algal oils can be sources of GLA, DGLA, AA, SA, EPA or DHA. The EFAs can be in any chemical form which is absorbed into the body and incorporated into body lipids. Such forms include but are not limited to free acids, sodium, potassium, lithium and other salts, triglycerides and other glycerides, cholesterol,

ethyl, methyl and other esters, amides, and phospholipids.

The vitamin K and the EFA when used for pharmaceuticals or nutritional supplements can be incorporated into any appropriate dosage form known to those skilled in the art. Such dosage forms include soft and hard gelatin capsules, tablets, microcapsules of various types, powders and carriers of various types, liquids, emulsions, micelles and any other forms. Flavourants, colourants, emulsifiers and conventional diluents and excipients may be included, alone or in combination.

When used in foods, the formulations may be prepared by increasing the concentration of vitamin K in the food to 1000 μg/100g or more. With some foods, such as milks, dairy products or vegetable oils, moderate amounts of EFAs may already be present in the natural food. Increasing the vitamin K content of such foods to a level above that present in any natural food is within the framework of the invention.

Alternatively, in addition to raising the vitamin K content of an EFA-containing food to over 1000 μg/100g, the desired EFA may also be added to the food to raise the amount provided. Natural and soy or other vegetable-based milks, soy and related products, dairy products including yogurts, cheeses, butters, margarines, or any other types of foods may all be treated in this way to provide a combination of vitamin K and an EFA.

These formulations may be used for general health purposes, or for specific conditions where either EFAs or both have been found to be helpful. These conditions include premenstrual and menstrual disorders, skin disorders, diabetes, elevated cholesterol and triglyceride levels, cardiovascular disorders, arthritis and any form of inflammatory disorder, respiratory disorders such as asthma, gastro-intestinal, urinary and reproductive system disorders in both sexes, mental, psychological and psychiatric disorders such as stress, chronic fatigue, behavioural problems in children and adults, depression, alcoholism and more serious psychiatric disorders such as schizophrenia and bipolar disorder, neurological disorders such as Parkinsonism, and any form of dementia and any other form of illness in which the combinations are found to be helpful. Osteoporosis and related disorders of bone and calcium metabolism are likely to provide particularly important uses for the invention.

Brief Description of the Figures

Fig. 1 The n-6 and n-3 essential fatty acids

Experimental Data

A woman with atopic dermatitis and with mild premenstrual syndrome was recommended to take 3g/day of evening primrose oil (EPO). EPO is a widely used nutritional supplement for these problems. It contains about 70% of linoleic acid, but more importantly contains 8-12% of GLA which can by-pass a block in the conversion of linoleic acid to GLA which

can occur in many situations, including atopic dermatitis, stress and menstrual disorders. Not everyone responds to EPO but this is an exceptionally safe nutritional supplement and does not cause any important side effects. However, to my surprise in this woman the EPO not only failed to have any therapeutic effect but caused a range of unusual side effects including facial reddening and rashes, a worsening of her dermatitis, gastro-intestinal disturbances and anxiety and depression. As a result of a series of investigations, she was found to have a vitamin K deficiency, possibly partly due to dietary problems and partly due to gastrointestinal infections which had necessitated the use of antibiotics which had probably changed her gut bacteria. The vitamin K deficiency was corrected by vitamin K1 supplements but this did not improve her skin or her premenstrual syndrome. As an experiment she was then cautiously given EPO again. This time there were no adverse effects at all, her skin improved and her premenstrual syndrome was resolved. This case suggested a hitherto unsuspected and important positive interaction between vitamin K and EFAs.

A second woman presented with severe menstrual cramps and mild premenstrual syndrome. I suggested that she should take a low dose of EPO (1g/day) to help with her premenstrual syndrome and a higher dose (4g/day) of a fish oil containing 23% of EPA and 8% of DHA to help with her menstrual cramps. Unfortunately she showed no response in either of her problems. She had a normal diet and no evidence of vitamin K deficiency but I wondered whether giving vitamin K

might help. She therefore took 2mg (2000 μg) per day of a vitamin K1 supplement for a month which also had no effect on her menstrual problems. However, on reintroducing the EPO and fish oil, her premenstrual syndrome disappeared completely and her menstrual pain was greatly reduced.

These cases show that vitamin K can greatly improve the therapeutic effects of EFAs, reducing any side effects and enhancing therapeutic effects.

Claims

1. Nutritional and pharmaceutical formulations comprising in combination a source of vitamin K and a source of at least one essential fatty acid (EFA), in which the concentration of vitamin K is not less than 1000 μg/100g.

2. Nutritional and pharmaceutical formulations according to claim 1, in which the concentration of vitamin K is not less than 100 μg/10g.

3. Nutritional and pharmaceutical formulations according to claim 1 or 2 which provide a daily dose between 50 μg and 100 mg vitamin K and between 50 mg and 100 g of the EFA.

4. Nutritional and pharmaceutical formulations according to any preceding claim in which the form of vitamin K used is phylloquinone (vitamin K1).

5. Nutritional and pharmaceutical formulations according to any preceding claim in which the EFA is selected from gamma-linolenic acid, dihomogammalinolenic acid, arachidonic acid and adrenic acid, and combinations of these EFAs.

6. Nutritional and pharmaceutical formulations according to any of claims 1-4 in which the EFA is selected from stearidonic acid, eicosapentaenoic acid, docosapentaenoic acid and docosahexenoic acid, and combinations of these EFAs.

7. Nutritional and pharmaceutical formulations according to any of claims 1-4 in which there is at least one n-6 EFA and at least one n-3 EFA present, the n-6 EFA(s) selected from gamma-linolenic acid, dihomogammalinolenic acid, arachidonic acid and adrenic acid, and combinations of these acids, and the n-3 EFA(s) selected from stearidonic acid, eicosapentaenoic acid, docosapentaenoic acid and docosahexaenoic acid, and combinations of these acids.

8. Nutritional and pharmaceutical formulations according to any preceding claim in which the active ingredient consists essentially wholly of EFA and vitamin K.

9. Nutritional and pharmaceutical formulations according to any of claims 1 to 7 further comprising one or more essential vitamins and/or minerals or one or more pharmaceutical drugs.

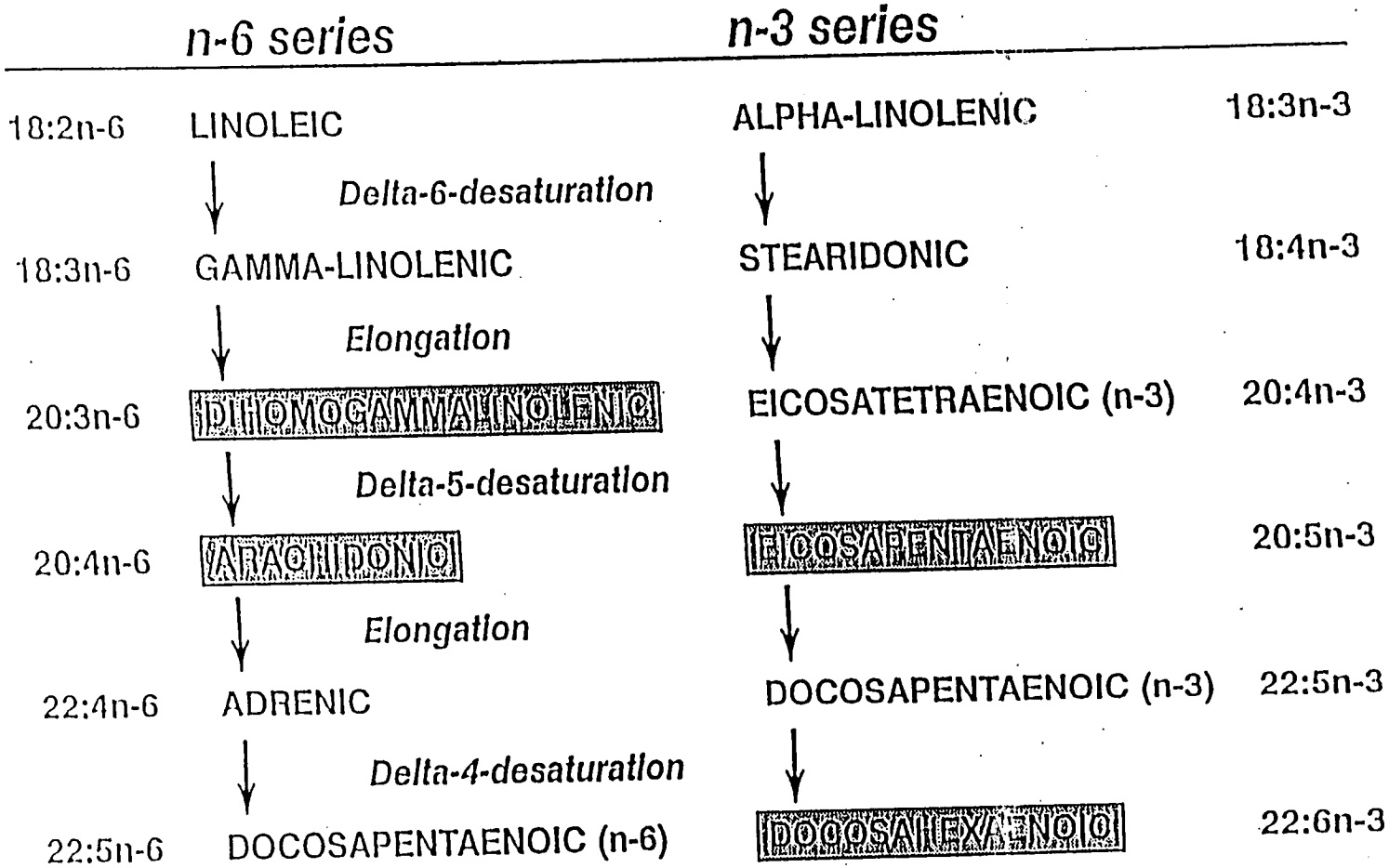
10. Foodstuff which already contain EFAs to which have been added vitamin K in an amount to raise the vitamin K content of the food to 1000 μg / 100 g food, or more.

11. Foodstuff according to claim 8 in which the specific EFA(s) content has been raised by the addition of one of more EFAs.

12. Foodstuff which naturally contains clinically or nutritionally small amounts of vitamin K and /

or EFA(s) to which has been added vitamin K and EFAs.

Fig. 1


n-6 series
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LINOLEIC
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Delta-6-desaturation
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GAMMA-LINOLENIC
STEARIDONIC
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Elongation
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EICOSATETRAENOIC (n-3)
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ARACHIDONIC
EICOSAPENTAENOIC
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Elongation
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ADRENIC
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1/1